



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 868 and 870

[Docket No. FDA-2012-N-1174]

Anesthesiology Devices; Reclassification of Membrane Lung for Long-Term Pulmonary Support; Redesignation as Extracorporeal Circuit and Accessories for Long-Term Pulmonary/ Cardiac Support

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: On its own initiative, based on new information, the Food and Drug Administration (FDA) is proposing to reclassify membrane lung devices for long-term pulmonary support, a preamendments class III device, into class II (special controls) for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. A membrane lung for long-term pulmonary support refers to the oxygenator component of an extracorporeal circuit used during long-term procedures, commonly referred to as extracorporeal membrane oxygenation (ECMO). Because circuit components used with the oxygenator are to be subject to the same regulatory controls, all of the device components used in an ECMO procedure are being considered in the scope of this proposed order, and the title and identification of the regulation will be revised accordingly to include extracorporeal circuit and accessories for long-term pulmonary/cardiac support.

DATES: Submit either electronic or written comments on this proposed order by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section XI of this document for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2012-N-1174, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following way:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2012-N-1174 for this order. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this

document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Angela Krueger,
Center for Devices and Radiological Health,
Food and Drug Administration,
10903 New Hampshire Ave.,
Bldg. 66, rm. 1666,
Silver Spring, MD 20993,
301-796-6380,
angela.krueger@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The FD&C Act, as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94-295), the Safe Medical Devices Act of 1990 (Public Law 101-629), the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115), the Medical Device User Fee and Modernization Act of 2002 (Public Law 107-250), the Medical Devices Technical Corrections Act of 2004 (Public Law 108-214), the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85), and Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness.

The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f) of the FD&C Act into class III without any FDA process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA (126 Stat. 1056) amended section 513(e) of the FD&C Act, changing the process for reclassifying a device from rulemaking to an administrative order.

Section 513(e) of the FD&C Act governs reclassification of preamendments devices. This section provides that FDA may, by administrative order, reclassify a device (in a proceeding that

parallels the initial classification proceeding) based upon “new information.” FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a preamendments device. The term “new information,” as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland Rantos v. United States Department of Health, Education, and Welfare, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent regulatory action where the reevaluation is made in light of newly available regulatory authority (see Bell v. Goddard, supra, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F.Supp. 382, 389-391 (D.D.C. 1991)) or in light of changes in “medical science.” (See Upjohn v. Finch, supra, 422 F.2d at 951.) Whether data before the Agency are past or new data, the “new information” to support reclassification under section 513(e) must be “valid scientific evidence,” as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Assoc. v. FDA, 766 F.2d 592 (D.C. Cir.), cert. denied, 474 U.S. 1062 (1985).)

FDA relies upon “valid scientific evidence” in the classification process to determine the level of order for devices. To be considered in the reclassification process, the valid scientific evidence upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending premarket approval application (PMA). (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).) Section 520(h)(4) of the FD&C Act, added by FDAMA, provides that FDA

may use, for reclassification of a device, certain information in a PMA 6 years after the application has been approved. This includes information from clinical and preclinical tests or studies that demonstrate the safety or effectiveness of the device but does not include descriptions of methods of manufacture or product composition and other trade secrets.

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers.

FDAMA added section 510(m) to the FD&C Act. Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act, if the Agency determines that premarket notification is not necessary to assure the safety and effectiveness of the device.

II. Regulatory History of the Device

On November 2, 1979 (44 FR 63387), FDA published a proposed rule for classification of membrane lungs for long-term pulmonary support as class III requiring premarket approval. The Anesthesiology Device Classification Panel recommended class III because the device is life sustaining and life supporting and sufficient information did not exist to determine the adequacy of general controls or to establish standards to provide a reasonable assurance of the safety and effectiveness of the device.

No comments were received on the proposed rule and on July 16, 1982 (47 FR 31130), a final rule was published for membrane lungs for long-term pulmonary support, classifying these devices as class III. In 1987, FDA published a final rule amending the codified language for this

device to clarify that no effective date had been established for the requirement for premarket approval for membrane lungs for long-term pulmonary support devices (52 FR 17732 at 17735; May 11, 1987). In 2009, FDA published an order under sections 515(i) and 519 of the FD&C Act (21 U.S.C. 360e and 360i) for the submission of safety and effectiveness information on a membrane lung for long-term pulmonary support (74 FR 16214; April 9, 2009). In response to that order, FDA received information from one device manufacturer.

III. Device Description

A membrane lung for long-term pulmonary support refers to the oxygenator component of an extracorporeal circuit used during long-term procedures, commonly referred to as an ECMO. An ECMO procedure provides assisted extracorporeal circulation and physiologic gas exchange of a patient's blood when an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life. The circuit is comprised of multiple device types, including, but not limited to, an oxygenator, blood pump, cannulae, heat exchanger, tubing, filters, monitors/detectors, and other accessories; the circuit components and configuration (e.g., arteriovenous, veno-venous) may differ based on the needs of the individual patient or the condition being treated. ECMO is intended for patients with acute reversible respiratory or cardiac failure, unresponsive to optimal ventilation and/or pharmacologic management.

Because circuit components used with the oxygenator can be appropriately regulated using the same set of regulatory controls, all of the device components used in an ECMO procedure are being considered in the scope of this proposed order as an extracorporeal circuit and accessories for long-term pulmonary/cardiac support.

IV. Proposed Reclassification

FDA is proposing that the device subject to this proposed order be reclassified from class III to class II. FDA is further proposing to revise the title and identification of the regulation to reflect all device components used in ECMO. In addition, FDA is proposing to remove this regulation from 21 CFR part 868, Anesthesiology Devices, and add the revised version to 21 CFR part 870, Cardiovascular Devices, to better align this device type with other similar types of cardiovascular devices and align the review responsibilities for this device type. FDA believes that these devices can be utilized to provide assisted extracorporeal circulation and physiologic gas exchange of a patient's blood when an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.

FDA believes that the identified special controls, in addition to general controls, are necessary to provide reasonable assurance of safety and effectiveness. Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and 21 CFR 860.130, based on new information with respect to the devices, FDA, on its own initiative, is proposing to reclassify this preamendments class III device into class II. The Agency has identified special controls under section 513(a) of the FD&C Act that would provide reasonable assurance of their safety and effectiveness. The new information includes the history of use of the circuit components, publicly available safety and effectiveness information (as described in Section VII of this document) and the relatively low incidence of adverse events, as discussed in the recommendations for reclassification from the device industry (available in docket FDA-2009-

M-0101 at <http://www.regulations.gov>). FDA believes that this information is sufficient to demonstrate that the proposed special controls can effectively mitigate the risks to health identified in section V of this document and that these special controls, in addition to the general controls, will provide a reasonable assurance of safety and effectiveness for ECMO devices.

FDA has considered membrane lung devices for long-term pulmonary support in accordance with the reserved criteria and decided that the device does require premarket notification. The Agency does not intend to exempt this proposed class II device from premarket notification (510(k)) submission as provided for under section 510(m) of the FD&C Act.

V. Risks to Health

After considering available information, including the recommendations of the advisory committee (panel) for the classification of these devices along with information submitted in response to the 515(i) order and any additional information that FDA has encountered, FDA has evaluated the risks to health associated with the use of extracorporeal circuits and accessories for long-term pulmonary/cardiac support and determined that the following risks to health are associated with its use:

- Thrombocytopenia. Blood platelets important to the clotting cascade may be damaged by use of the device, resulting in a tendency toward increased bleeding.
- Hemolysis. Red blood cells may be damaged by mechanical, material, or surface features of the extracorporeal circuit.
- Thrombosis/thromboembolism. Blood clots may form within the extracorporeal circuit due to inadequate blood flow.
- Hemorrhage. To keep blood from clotting in the extracorporeal circuit, anticoagulants are generally used and may cause increased bleeding during the procedure.

- Hemodilution. Dilution of the patient's blood may be caused by the priming of the ECMO circuit.
- Inadequate gas exchange. Mechanical failure of the circuit components may result in inadequate gas exchange.
- Loss of mechanical integrity. Weakness in the connections or construction of the circuit components could lead to leaks in the extracorporeal circuit.
- Gas embolism. Air may be introduced into the extracorporeal circuit and result in a gas embolism.
- Adverse tissue reaction. The patient-contacting materials of the device may cause an adverse immunological or allergic reaction in a patient if the materials are not biocompatible.
- Infection. Defects in the design or construction of the device preventing adequate cleaning and/or sterilization may allow pathogenic organisms to be introduced and may result in infection.
- Mechanical injury to access vessels. Mechanical injury to vessels may be caused acutely during access, or over time due to the long-term duration of use.

VI. Summary of Reasons for Reclassification

FDA believes that extracorporeal circuits and accessories for long-term pulmonary/ cardiac support should be reclassified into class II because special controls, in addition to general controls, can be established to provide reasonable assurance of the safety and effectiveness of the device. In addition, there is now adequate effectiveness information sufficient to establish special controls to provide such assurance for conditions where imminent death is threatened by

cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.

FDA is proposing to rename this device to “Extracorporeal circuit and accessories for long-term pulmonary/cardiac support”; the current classification regulation for this device is referred to as “membrane lung for long-term pulmonary support.” For clarity, the new title for this proposed order will be removed from 21 CFR part 868 and redesignated to 21 CFR part 870. Section 870.4100 will be added to reflect all device components used in ECMO.

VII. Summary of Data upon Which the Reclassification Is Based

Since the time of the Panel recommendation, sufficient evidence has been developed to support a reclassification of extracorporeal circuits and accessories for long-term pulmonary/cardiac support to class II with special controls for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. FDA is familiar with the risks associated with the use of the components of the extracorporeal circuit because the same components are used for short-term use (durations less than 6 hours) for cardiopulmonary bypass. In addition, the Extracorporeal Life Support Organization registry data (Ref. 1), which provides information on over 28,000 ECMO procedures performed since 1987, and reviews of institutional experience (Ref. 2) demonstrate a favorable benefit-risk profile for extracorporeal circuits and accessories when used for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.

VIII. Proposed Special Controls

FDA believes that the following special controls, in addition to general controls, are sufficient to mitigate the risks to health described in section V of this document:

- The design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use;
- The device must be demonstrated to be biocompatible;
- Sterility and shelf life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;
- Nonclinical performance evaluation of the device must demonstrate a reasonable assurance of safety and effectiveness for mechanical integrity, durability, and reliability;
- In-vivo evaluation of the device must demonstrate device performance; and
- Labeling must include a detailed summary of the nonclinical and clinical evaluations pertinent to use of the device and adequate instructions with respect to anticoagulation, circuit set up, and maintenance during a procedure.

In addition, under 21 CFR 801.109, the sale, distribution, and use of this device are restricted to prescription use.

IX. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Paperwork Reduction Act of 1995

This proposed order refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of

Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 812 are approved under OMB control number 0910-0078; the collections of information in part 807, subpart E, are approved under OMB control number 0910-0120; the collections of information in 21 CFR part 814, subpart B, are approved under OMB control number 0910-0231; and the collections of information under 21 CFR part 801 have are under OMB control number 0910-0485.

XI. Proposed Effective Date

FDA is proposing that any final order based on this proposal become effective 30 days after date of publication of the final order in the Federal Register.

XII. Comments

Interested persons may submit either electronic comments to <http://www.regulations.gov> or written comments regarding this document to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

XIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>.

1. Fleming, G. M., J. G. Gurney, J. E. Donahue, et al., "Mechanical Component Failures in 28,171 Neonatal and Pediatric Extracorporeal Membrane Oxygenation Courses From 1987 to 2006," Pediatric Critical Care Medicine Journal, vol. 10, pp. 439-

444, July 2009.

2. Cook, L. N., "Update on Extracorporeal Membrane Oxygenation," Paediatric Respiratory Reviews, vol. 5, suppl. A, pp. S329-S337, 2004.

List of Subjects in 21 CFR Parts 868 and 870

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 868 and 870 be amended as follows:

PART 868--ANESTHESIOLOGY DEVICES

1. The authority citation for 21 CFR part 868 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

§ 868.5610 [Removed]

2. Remove § 868.5610.

PART 870--CARDIOVASCULAR DEVICES

3. The authority citation for 21 CFR part 870 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

4. Add § 870.4100 to subpart E to read as follows:

§ 870.4100 Extracorporeal circuit and accessories for long-term pulmonary/cardiac support.

(a) Identification. An extracorporeal circuit and accessories for long-term pulmonary/cardiac support (>6 hours) is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood in conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. An

acute reversible or treatable cause of respiratory and/or cardiac failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical or ventilation therapy. The main components of the system include the console (hardware), software, and disposables, including but not limited to, an oxygenator, blood pump, heat exchanger, cannulae, tubing, filters, and other accessories (e.g., monitors, detectors, sensors, connectors).

(b) Class II (special controls). The special controls for this device are:

- (1) The design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use;
- (2) The device must be demonstrated to be biocompatible;
- (3) Sterility and shelf life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;
- (4) Non-clinical performance evaluation of the device must provide a reasonable assurance of safety and effectiveness for mechanical integrity, durability, and reliability;
- (5) In-vivo evaluation of the device must demonstrate device performance; and
- (6) Labeling must include a detailed summary of the nonclinical and clinical evaluations pertinent to use of the device and adequate instructions with respect to anticoagulation, circuit set up, and maintenance during a procedure.

Dated: January 2, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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